Wheat allergy in celiac children

To the Editor,

Gluten is the main structural protein complex of wheat with equivalent toxic proteins found in other cereals (rye, barley, and oats) which are responsible for different immunologic responses with different clinical expressions of disease. The spectrum of gluten-related disorders has been classified according to pathogenic, clinical, and epidemiological differences in three main forms: (i) wheat allergy (WA), an IgE-mediated disease; (ii) autoimmune disease, including celiac disease (CD), dermatitis herpetiformis, and gluten ataxia; and (iii) possibly immune-mediated, gluten sensitivity (1). WA is an immunologic Th2 response with typical manifestations which can vary from dermatological, respiratory, and/or intestinal to anaphylactic reactions. In contrast, CD is an autoimmune disorder, a gliadin-specific T-cell response which is enhanced by the action of intestinal tissue transglutaminase (tTG), with a wide clinical spectrum including symptomatic cases with either intestinal (e.g., chronic diarrhea, weight loss) or extraintestinal features (e.g., anemia, osteoporosis, neurologic disturbances) and silent forms that are occasionally discovered as a result of serological screening (1).

We studied wheat allergy in two children with early diagnosis of CD, who developed immediate allergic symptoms after eating small amounts of wheat flour.

Case 1

A 19-month-old boy, suffering atopic dermatitis and wheezing from 3 months of age, developed allergic symptoms, urticarial with lip edema and vomiting 30 min after boiled egg or lentil ingestion, and urticarial with bronchospasm 15 min after fish ingestion. He tolerates any other food including cereals (wheat, rye oats, rice, and corn) and peeled fruits including peach. We demonstrated specific IgE antibodies to fish, egg, and legumes and the infant started a fish, egg, and legume-free diet. Six months after that, he suffered chronic diarrhea and weight loss. His mother had a diagnosis of CD, and all family members have the allelic combination HLA-DQA1 05 cis DQB1 02.

Table 1 Clinical data of study patients. Sex; age diagnosis of CD, WA, and grass pollen allergy; and diagnostic criteria of CD (digestive symptoms, tTG IgA, HLA genes)

Sex	Case 1 M	Case 2 F
Celiac Disease Diagnosis		
Age	25 months	17 months
Abdominal pain	Yes	Yes
Abdominal distension	Yes	Yes
Diarrhea and vomiting	Yes	Yes
Weight loss	Yes	Yes
tTG IgA (0–7 UA/L normal)	> 100 UA/L	> 100 UA/L
Biopsy results	Type 3c Marsh-Oberhuber	Type 3c Marsh-Oberhuber
HLA-DQ	DQA1*05 DQB1*02	DQA1*05, DQB1*02
Age of onset wheat allergy	4 years	12 years
Age of onset grass pollen allergy	8 years	6 years

Finally, the patient resulted with a diagnosis of CD (Table 1). He started a gluten-free diet (GFD), and 3 months later, his weight gain and his intestinal symptoms disappeared. When he was 4 years old, he had three episodes with abdominal pain, vomiting, and hypotension within 10 min of ingesting foods with hidden wheat flour. Then, serum-specific IgE to wheat was demonstrated.

Finally, at the age of eight, he developed spring rhinitis and asthma and we demonstrated specific IgE to grass pollens. At this time, he was tolerating baked egg and canned tuna, but he had bronchospasm with steam fish such as hake, and even hake IgE was increased. White egg IgE and lentil IgE decreased, for this reason open controlled challenges with both boiled white egg and lentils, were performed and resulted in immediate development of urticaria, lip edema, and vomiting.

Case 2

A 14-month-old girl suffering from chronic diarrhea and weight loss was diagnosed with CD (Table 1). She had a rapid clinical response after starting GFD. Three months later, her weight had improved, becoming normal. She did not have any relative with a history of CD. She did not have allergic symptoms with any food and tolerates corn, rice, and peach.

At age six, she began with spring seasonal allergic rhinitis. Finally at seven, ten minutes after eating a soft candy, she developed nasal pruritus, facial angioedema, dyspnoea, and cough; this reaction was controlled with dexclorfeniramine, corticosteroids, and adrenaline treatment. Ingredients on the candy label were assessed as possible allergens, and the ingredients of the label were studied.

Methods

Our patients and their parents gave their consent.

Skin prick by prick tests with candy '*Lengua verde*' (Haribo España, S.A.) were carried out in patient 2 and in one non-allergic patient. Ingredients on '*Lengua verde*' label were investigated.

Skin prick tests (SPT) were performed in both cases with the following: flour cereals (wheat, rye, barley, oats, corn and rice), gluten, gliadin, a battery of airborne allergens using commercial extracts, and histamine and saline solution as positive and negative controls (ALK-Abelló Laboratories, Madrid, Spain). Skin tests were considered positives if average diameter was equal or greater than the histamine diameter and at least 3 mm more wide than the negative control.

Total and specific IgE to cereals, gluten, gliadin, airborne allergens, and their determinants was assessed by ImmunoCAP and microarrays (ISAC IgE) (Thermo Fisher, Uppsala, Sweden).

Results

Table 1 shows clinical data and the results of CD study, and Table 2 shows the results of specific IgE in both cases.

Table 2 ImmunoCAP and Microarrays (ISAC) of wheat seed and grass pollen allergens

	Case 1	Case 2
IgE kU/L (CAP)		
Total IgE	178	825
Wheat flour	2.99	15.3
Rye	1.91	8.78
Gluten	1.42	7.45
rTri a 14 (LTP)	2.69	14
rTri a 19 (ω5-gliadin)	0.02	0.20
Phleum	40.4	56.8
Microarrays ISAC (ISU)		
nTri a aA_TI (α-amilasa)	0.0	0.5
rTri a 19.0101 (ω5-gliadin)	0.0	0.0
Lipid Transfer Proteins LTP		
rTri a 14 (LTP)	4.3	17.3
rPru p 3	0.1	0.2
rCor a 8	0.4	0.0
nJug r 3	0.0	0.0
rAra h 9	0.0	0.0
n Art v 3	0.2	0.0
n Ole e 7	0.0	0.0
r Pla a 3	0.2	0.0
Grass components		
nCyn d 1	8.8	8.8
rPhl p 1	22.0	66.4
rPhl p 2	0.0	7.7
rPh1 p 4	0.0	1.1
rPh1 p 5	0.0	0.0
rPh1 p 6	0.0	0.0
rPh1 p 7	0.1	0.0
rPh1 p 11	0.3	0.8

Case 1

SPT and specific IgE resulted positive to airborne allergens (grasses and Alternaria), wheat flour, gluten, and gliadin; and negative to rye, corn and oat flour.

Case 2

Skin prick by prick tests to soft candy 'Lengua verde' (Haribo), responsible for the reaction in this patient, resulted positive (average diameter 11 mm 'Lengua verde', 5 mm histamine, and 0 mm saline solution) in the patient, but negative in the control no allergic people (0 mm 'Lengua verde', 4 mm histamine, and 0 mm saline solution).

Ingredients of candy label 'Lengua verde' (Haribo España, S.A.) were as follows: sugar, glucose and fructose syrup, corn starch, sorbitol syrup, wheat flour, citric acid, dyes E-104 and E-131, and emulsifier E-147. SPT to each component of the 'Lengua verde' candy (10 and 20 mg/ml) resulted negative except wheat flour.

SPT resulted positive to gluten, gliadin, wheat, rye, corn and oat flour, lupine, and buckwheat; nuts (hazelnut and almond); and pollens (phleum, olive, and mugwort).

Discussion

We studied two children with atopic dermatitis suffering early symptomatic celiac disease with classical intestinal damage which involves substantial alterations of the intestinal barrier with increased permeability, which favor the passage of allergens. These conditions are risk factors in the development of a specific IgE response to food allergens. Both of our patients achieved a rapid control when starting a gluten-free diet. Later, they developed allergic reactions immediately after inadvertent dietary transgressions with wheat.

Wheat allergy is the one IgE-mediated reaction; in early childhood, it is overcome within 3–5 years of age and usually is associated with atopic dermatitis and sensitization or allergy to other foods. Our patients had atopic dermatitis, and case 1 had hen's egg and fish allergy too. But, unlike wheat allergic non-celiac children, both of our patients developed wheat allergy later. Three different situations could be possible: (i) Our patients could have specific wheat IgE coinciding with the diagnosis of their celiac disease, and they could have showed immediate digestive symptoms masked by symptoms of their CD; (ii) despite having specific IgE, the continuous ingestion of wheat could have maintained a mechanism of desensitization, which could have avoided the allergic symptoms before starting a GFD; and (iii) the specific IgE response to wheat could have developed after starting GFD by inadvertent ingestion of wheat.

Wheat-related allergens include various components: A salt-soluble protein IgE response is associated with baker's asthma, particularly to α-amylase/trypsin inhibitor family and lipid transfer protein, peroxidase, and other soluble enzymes in wheat flour (2). Wheat-dependent exercise-induced anaphylaxis (WDEIA) is produced by a salt-insoluble protein IgE response, particularly to ω5-gliadin. However, both protein fractions could be responsible for food allergy to wheat (3). Tatham and Shewry (2) observed that all patients with anaphylaxis or WDEIA and 55% of those with urticaria had IgE to ω5-gliadins (part of the gluten protein fraction).

We identified Tri a 14 (wheat LTP) as the responsible allergen of wheat allergy in our patients. LTPs are abundant proteins in cereal grains; Battais et al.(4) reported that 28% of 60 patients with wheat food allergy showed IgE reactions to purified wheat LTP, and Palacin et al.(5) reported wheat LTP as an inhalant allergen in baker's asthma. In a study, Pastorello et al. (6) found that IgE binding to glutenins was observed in approximately 72% of patients with wheat allergy; they identified Tri a 14 as a wheat allergen in nine of 22 patients with wheat-induced food allergy; and they observed cross-reactivity between corn (Zea m14), peach (Pru p 3), and rice LTP, but not with Tri a 14 (7).

Our patients developed grass pollen allergy, but none of them had specific IgE to LTP pollen allergens. Jones et al. (8) did not find clinically significant cross-reactivity between cereals and grasses in children with confirmed wheat allergy by oral challenges. Pastorello et al. (6), using sera of 22 European patients with wheat food allergy, showed a lack of cross-reactivity between grass pollen allergens and nsLTP or α-amylase inhibitors. Constantin et al. (9) identified rPhl p 1 and rPhl p 5 as marker allergens specific to grass pollen allergy. The immunoglobulin E reactivity profiles in our cases supported that wheat allergy is specific to Tri a 14 and it is not a cross-reactivity secondary to other food allergy in a LTP syndrome.

To the best of our knowledge, only one case of wheat allergy has been reported in a celiac latent disease (10). This is the first report of classic symptomatic celiac disease associated with wheat allergy. We concluded that celiac patients with immediate symptoms coinciding with diet transgression could have a wheat IgE response with an association of CD and WA.

M. F. Martín-Muñoz , D. Rivero , A. Díaz Perales , I. Polanco & S. Quirce

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Recovery from food protein-induced enterocolitis syndrome caused by fish

To the Editor,

Adverse reactions to food in childhood are very frequent. Often they involve the skin, airways and gastrointestinal tract, and in severe cases circulation can also be affected, with a drop in blood pressure. These reactions can be either immunoglobulin E (IgE) dependent or not. In IgE-dependent reactions, IgE antibodies to the food are detected in blood tests or skin prick tests. The pathomechanism behind non-IgE involvement reactions is, however, still not known. A defined type of non-IgE reaction to food is food protein-induced enterocolitis syndrome (FPIES). This entity was first evaluated in 1967 when Gryboski identified several children with chronic gastrointestinal allergy to milk which manifested as diarrhoea, vomiting and colic. The symptoms disappeared when proteins causing the symptoms were eliminated from the diet and recurred when they were reintroduced (1).

Typical symptoms of FPIES usually occur 30 min to 4 h after ingestion of the offending food protein. The most commonly responsible trigger foods are milk and soya proteins, but a variety of different proteins found in solid foods (e.g. rice, oats, barley, meat, fish, vegetables, fruits) can also cause this reaction (2). The symptoms of FPIES include vomiting, diarrhoea, bloody diarrhoea, lethargy and pallor, and even hypovolemic shock. Skin symptoms such as urticaria and pruritus as well as airways symptoms are absent (3).

Clinical history is the basis for diagnosis of FPIES but in cases where there is doubt about the diagnosis, food provocation can be considered. Furthermore, absence of increased levels of specific IgE antibodies to food strengthens the diagnosis (4).

The natural history of FPIES provoked by milk and soya is extensively studied and results show a good recovery rate. In a recent study, 90% of the included children tolerated milk by age of 3 (5). Development of natural tolerance for solid foods is, however, limited. The incidence of FPIES caused by fish seems to differ between countries. In the USA and Australia, reactions to fish are very seldom seen, but in a report from Italy, FPIES reaction to fish is the most common reaction to solid food (4). The natural history of FPIES in children following ingestion of fish is sparely studied, and only a few reports have been published (4, 6, 7). In this study, we evaluate the development of tolerance in children with FPIES caused by fish protein.

At our allergy clinic, we identified patients with a history of unexplained vomiting, at least in two occasions after eating fish. Ten children, two boys and eight girls, born between 1996 and 2002, were identified. All children fulfilled criteria for FPIES (8) as they had reactions after eating codfish, but they had no skin or respiratory symptoms. Vomiting started between 30 min and 4 h after fish intake. Skin prick tests and/or blood tests for specific IgE for codfish were negative in all patients. Atopy patch testing (APT) was not performed. Nine children were between 9 and 30 months old when they had their first reaction after eating fish, with a mean age of 18 months. One child had been born moderately preterm, and introduction to fish was delayed until 4 years of age for unknown reasons. The severity of reaction ranged from vomiting only (n = 8) to vomiting with diarrhoea (n = 1) and severe symptoms in need of intravenous treatment with fluids (n = 1). Data are missing concerning other symptoms such as lethargy and pallor. Besides the reaction to fish, three of our patients had vomiting after consuming chicken and one of these also after eating egg. Four children had a history of classic FPIES, and further diagnostic evaluation was not performed. In six children with vague history, an oral provocation with codfish was undertaken. Five reacted with symptoms in the same way as before. In one of these children, provocation was delayed to 4 years of age and at that time no reactions were observed. This child had eliminated fish from their diet for 2 years. One of the children reacted with vomiting at age 4, but a new provocation 1 year later was negative. We decided to follow the children by administering a questionnaire to them at 11–17 years of age, to describe the recovery from FPIES caused by fish and also to record development of symptoms of IgE-mediated allergy. This study has not been evaluated by the ethics committee as it was performed as part of our clinical work.

We received completed questionnaires for eight children. Five had developed tolerance to fish at between 4 and 8 years